REMARKS

Amendments

Claims 1 and 68 are amended to further define the proviso clauses. See, e.g., the original claims and the exemplified compounds. As a result of the amendments to claim 1, claim 2 is cancelled, without prejudice, and claims 17, 21, and 23 are amended to be consistent with the language of claim 1. Claim 70 is amended to be consistent with the language of claim 68. Claims 1, 33, 34, 68, and 71 are amended to address issues raised in the 112, second paragraph rejection. Claim 35 is amended to be in independent form and claim 36 is amended to depend from claim 35. Claims 75, 78, and 81 are amended to depend from claim 68, rather than cancelled claims. Claims 38-42, 46-48, 50, 51, 54, 56, 57, 59, and 82 are cancelled, without prejudice, to further prosecution and reduce the number of issues.

New claims 83-99 are directed to further aspects of the invention and are supported throughout the disclosure. See, e.g., page 48, line 22-page 49, line 11, the exemplified compounds, and the original claims.

Rejection under 35 USC 103(a) in view of Kelley et al. (1990)

Claims 1-4, 6, 10, 16, 17, 21, 27-32, 60, 61, 68 and 70 are rejected as allegedly being obvious in view of the 1990 article by Kelley et al. This rejection is respectfully traversed.

In the rejection the Examiner initially refers to compound 2 of Kelley et al., 6-methylamino-9-(4-methylbenzyl)-2-trifluoromethylpurine and argues that this compound renders the corresponding 6-ethylamino compound obvious based on homology. However, the rejection fails to establish that one of ordinary skill in the art would consider methylamino and ethylamino to be adjacent members of a homologous series. In the numerous cases cited by the Examiner, the compounds involved differed by one or two methyl groups wherein the alkyl groups in question were substituents attached to a carbon ring atom or a carbon atom of a chain. The rejection fails to set forth any reason that there is an expectation of homology with respect to the groups methylamino and ethylamino. In any event, the claims do not encompass compound 2 of Kelley et al. or

the corresponding ethylamino compound.

The rejection then refers to compound 11 of Kelley et al., i.e., 6-cyclopropylamino-9-(4-methylbenzyl)-2-trifluoromethylpurine, and argues that this compound renders the corresponding 9-(4-ethylbenzyl)compound obvious on the basis of homology and 9-(3-methylbenzyl) and 9-(2-methylbenzyl) on the basis of structural isomerism. The claims do not encompass compound 11 of Kelley et al. or the corresponding 9-(4-ethylbenzyl), 9-(3-methylbenzyl), and 9-(2-methylbenzyl) compounds.

Thereafter, the rejection refers to compounds 8, 9, 12, 14, 15, 17, 18, 21 and 22 of Kelley et al. All of these compounds exhibit disubstituted-amino groups at the 6-position wherein one of the substituents is a methyl group. The Examiner argues that these compounds render obvious the corresponding monosubstituted-amino compounds in which the methyl group is absent. The claims do not encompass compounds 8, 9, 12, 14, 15, 17, 18, 21 and 22 of Kelley et al. or the corresponding monosubstituted-amino compounds.

In view of the above remarks, it is respectfully submitted that Kelley et al. fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103(a) in view of Bourguignon et al.

Claims 1-3, 6, 10, 16, 17, 21, 27-32, 35, 38-42, 46-48, 50, 51, 54, 56, 57, and 59-61are rejected as allegedly being obvious in view of the article by Bourguignon et al.

Referring to the formula shown at the top of Table I of Bourguignon et al., in compound 6i, NR_1R_2 is amino, $-CH_2-R$ is benzyl, and R_3 is CF_3. The Examiner argues that this compound renders obvious the corresponding methylbenzyl compounds based on homology. However, compound 6i of Bourguignon et al. and the corresponding methylbenzyl compounds are not encompassed the claims.

It is further alleged that compound 6i renders obvious the chain homolog where $-CH_2-R$ is phenethyl. The rejection fails to present any evidence that one of ordinary skill in the art would consider benzyl and phenethyl to be adjacent members of a homologous series. In an event, the claims do not encompass compound 6i or the corresponding

phenethyl compound.

The rejection next refers to compound 6d of Bourguignon et al., wherein NR_1R_2 is methylamino, $-CH_2-R$ is 2-F-benzyl, and R_3 is CF_3. The Examiner argues that this compound renders obvious the corresponding compounds in which NR_1R_2 is ethylamino or butylamino. As discussed above, the rejection fails to set forth any reason that there is an expectation of homology with respect to the groups methylamino and ethylamino. In any event, the claims do not encompass compound 6d of Bourguignon et al., or the corresponding ethylamino or butylamino compound.

Thereafter, the rejection refers to compound 6k of Bourguignon et al., wherein NR_1R_2 is methylamino, $-CH_2-R$ is phenethyl, and R_3 is CF_3, and compound 6l, wherein NR_1R_2 is methylamino, $-CH_2-R$ is methyl, and R_3 is CF_3. The Examiner apparently argues that these compounds render obvious the corresponding compounds in which NR_1R_2 is ethylamino or butylamino. As discussed above, the rejection fails to set forth any reason that there is an expectation of homology with respect to the groups methylamino and ethylamino. In any event, the claims do not encompass compounds 6k and 6l of Bourguignon et al., or the corresponding ethylamino and butylamino compounds.

In view of the above remarks, it is respectfully submitted that Bourguignon et al. fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103(a) in view of Kelley et al. (1997)

Claims 1, 2, 4, 27-29, and 60 are rejected as allegedly being obvious in view of the 1997 article by Kelley et al.

In the rejection, the Examiner refers to compounds 54, 60, and 80 of Kelley et al. (1997). In compound 80, the substituent in the 6-position of the purine ring is NH-cyclopropyl and the substituent in the 9-position of the purine ring is cyclopropylmethyl. The Examiner argues that this compound renders obvious the compound wherein the substituent in the 9-position is $-CH(CH_3)$-cyclopropyl, further citing compounds 54 and 60. The claims do not encompass compound 80 of Kelley et al., or the corresponding $-CH(CH_3)$-cyclopropyl compound.

In view of the above remarks, it is respectfully submitted that Kelley et al. fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

Obviousness-Type Double Patenting Rejection in view of Serial No. 10/636,996

Claims 1-3, 6-36, 38-42, 46-48, 50, 51, 54, 56, 57, 59-61, 68, 70, 72, 73, and 80-82 are rejected as allegedly being obvious in view of "claim 1 and others" of Serial No. 10/636,996. This rejection is respectively traversed.

The claims of Serial No. 10/636,996 have been amended and do not read on the 6-monomethylamino group as asserted in the rejection. Withdrawal of the rejection is respectfully requested.

Obviousness-Type Double Patenting Rejection in view of Serial No. 10/845,354

Claims 38-42, 46-48, 50, 51, 54, 56, 57, 59-61, 70, 72, and 75-79 are rejected as allegedly being obvious in view of claims 2-53 and 62-81 of Serial No. 10/845,354. This rejection is respectively traversed.

All of the claims pending in Serial No. 10/845,354 are method claims directed to enhancing cognition in a patient, treating patients suffering from cognition impairment or decline, or treating patients suffering from memory impairment. The rejection fails to establish how these method claims establish obviousness-type double patenting as to claims directed to different classes of patentable subject matter such as compositions (compare applicants' claims 60-61) and compounds (compare applicants' claims 72 and 77).

Further, it is noted that the rejection is not applied to applicants' method claim 68, directed to methods of treating a patient suffering from an allergic or inflammatory disease. The rejection therefore fails to establish how the claims pending in Serial No. 10/845,354 establish obviousness of applicants claim 70, which is also a method claim directed to treating a patient suffering from an allergic or inflammatory disease.

In any events, to further prosecution, all remaining method claims pending in this application are, like claim 68, directed to methods of treating a patient suffering from an allergic or inflammatory disease. Therefore, withdrawal of the rejection for obviousness-

type double patenting is respectfully requested.

Rejection under 35 USC 112, second paragraph

Claims 1-5, 16-29, 33, 34, 38-42, 46-48, 50, 51, 54, 56, 57, 59-61, 68, 70, 71, and 80-82 are rejected on grounds of indefiniteness. This rejection is respectfully traversed.

The Examiner argues that alkyl ether, hydroxamic acid, and carboxamide are impossible for group R^2 because these are compounds and have no valences. Applicants' respectfully disagree. One of ordinary skill in the art, in reading the definition of R^2, would recognize that this group is a radical and thus must have a valency. Further, one of ordinary skill in the art would undeniably recognize that the "alkyl ether" recited in the claims is an alkoxyalkyl group since applicants' specification expressly defines it as such. See page 31, lines 23-24 of the specification where alkyl ether is explicitly defined as a C_3 to C_{12} alkoxyalkyl radical, and methoxyethyl, ethoxyethyl, and methoxypropyl are listed as examples.

The same is true for the substituents on aryl or heteroaryl groups. Thus, one of ordinary skill in the art would not interpret the terms hydroxamic acid and carboxamide in the manner suggested in the rejection, that is without a valency. Instead, one of ordinary skill in the art would recognize that the hydroxamic acid substituent is the group -C(O)-NHOH, and the carboxamide substituent is -C(O)-NH_2. Nothing in the rejection provides any support for the allegation that one of ordinary skill in the art would reasonably interpret these substituents in some other manner.

Also, as can be seen from the attached excerpt from Grant and Hackh's Chemical Dictionary, a hydroxamic acid is defined as an organic compound containing the radical -C(O)-NHOH. Thus, one of ordinary skill in the art would recognize that a hydroxamic acid substituent would be the radical -C(O)-NHOH. Furthermore, Grant and Hackh's Chemical Dictionary defines carboxamide as the group -C(O)-NH_2.

The rejection also argues that oxo is not a proper substituent for aryl or heteroaryl. To further prosecution, applicants have deleted oxo as a heteroaryl substituent.

As for "acyl," this term is clearly not indefinite. It is specifically defined in the specification at page 34, lines 1-5 as being an alkanoyl radical having 1 to 6 carbon atoms in which the alkyl portion can be substituted by halogen, alkyl, aryl and/or alkoxy, or an aroyl radical having 7 to 15 carbon atoms in which the aryl portion can be substituted by, for example, halogen, alkyl and/or alkoxy.

As for the starting material for claim 71, applicants have corrected the typographical error. See, e.g., the text bridging pages 41-42 of the specification.

In the rejection, it is argued that "PDE4" is unclear because there are four types of PDE4, which can occur in isoforms. Breadth is not indefiniteness. See, e.g., *In re Gardner*, 166 USPQ 138 (CCPA 1970). One of ordinary skill in the art can readily recognize the literal scope of claim 68 encompasses method embodiments wherein the inflammatory disease results from elevated phosphodiesterase 4 levels, whether the elevated phosphodiesterase 4 levels are PDE4A levels, PDE4B levels, etc. Further, it is argued in the rejection that the scope of "disease resulting from decreased cyclic AMP levels" is unknown because one does not know which inflammatory diseases result from decreased cyclic AMP levels or from elevated phosphodiesterase 4 levels or both. However, the rejection fails to support this assertion. Nor does the rejection establish that at one of ordinary skill in the art can not readily determine, in a patient suffering from an inflammatory disease, whether that patient is experiencing decreased cyclic AMP levels or elevated phosphodiesterase 4 levels or both, and whether a treatment which increases cyclic AMP levels or decrease phosphodiesterase 4 levels or both will treat that inflammatory disease. Here again, breadth is not indefiniteness. See, e.g., *In re Gardner*.

In view of the above remarks, it is respectfully submitted that the language of the claims is sufficiently definite, and that one of ordinary skill in the art can readily ascertain whether a given embodiment is within or outside the literal scope of the claims. Nothing more is required under the statute. Withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 112, first paragraph

Claims 38-42, 46-48, 50, 51, 54, 56, 57, 59-61, 68, 70, 72, 73, and 80-82 are rejected on grounds of lack of enablement. This rejection is respectfully traversed.

To further prosecution and reduce the number of issues, claims 38-42, 46-48, 50, 51, 54, 56, 57, 59, and 82 are cancelled. Cancellation of these claims is not to be construed as acquiescence to the arguments presented in the rejection.

Claims 60-61 are composition claims. Claims 72-73 are compound claims. The rejection fails to represent any rational as to why these claims are not enabled. The only claims specifically mentioned in the rejection are method claims 47, 54, 57, and 68.

The rejection primarily argues that the scope of inflammatory diseases is too broad. At pages 15-33 of the Office Action, the Examiner describes a variety of inflammatory diseases, and the alleged typically treatments, or, in some cases, the alleged lack of treatment. However, the rejection cites no support for these disease descriptions or the asserted treatments.

Applicants have cited numerous references that demonstrate that the use of PDE 4 inhibitors for treating inflammation is extremely well known in the art. The comments in the rejection do not address the recognition in the art or the evidence in support thereof.

Moreover, method claims are inherently functional. In other words, the literal scope of the method claims encompass only those embodiments that achieve the specified function. See, e.g., *In re Angstadt*, 190 USPQ 214 (CCPA 1976) and *Dinn-Nguyen et al.*, 181 USPQ 46 (CCPA 1974).

The assertions presented in the rejection present no reason to doubt that PDE4 inhibitors can be used for the treatment of inflammation in a patient suffering from an inflammatory disease associated with decreased cyclic AMP levels, elevated phosphodiesterase 4 levels, or both, especially since one of ordinary skill in the art is well aware of the use of PDE4 inhibitors for just such treatments. The "state of the art" is that the art clearly recognizes the use of PDE4 inhibitor compounds to treat inflammation and associated diseases.

It is noted that enablement under 35 USC 112, first paragraph, for pharmaceutical

treatments, does not necessitate that the treatment be approved by the FDA with respect to either efficacy or safety. See, e.g., *In re Brana,* 51 F.3d 1560,____, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995) and *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Thus, an assertion that PDE4 inhibitors are not presently approved by the FDA for treating a given inflammatory disease does not establish any reason to doubt that PDE4 inhibitors can be used to treat that inflammatory disease, especially when the art recognizes that PDE4 inhibitors can be used to treat that inflammatory disease.

An application disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph 35 U.S.C. § 112, unless there is reason to doubt the objective truth of statements contained therein relied on for enabling support. *In re Brana,* 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). *Fiers v. Revel,* 984 F.2d 1164, 24 USPQ2d 1601 (Fed. Cir. 1993). Furthermore, as stated in *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (CCPA 1971), the PTO must have adequate support for its challenge to the credibility of applicant's statements of utility. See also *In re Bundy*, 209 USPQ 48 (CPA 1981).

So, to establish non-enablement, the rejection can not merely assert that the treatment of inflammation is non-enabled. Instead, the rejection must present reason why one would doubt that inflammation can be treated using applicants' PDE4 inhibitor compounds, despite the fact that, as shown above, the art clearly recognizes the use of PDE4 inhibitors to treat inflammation and associated diseases.

To establish the requisite objective enablement under the 35 USC 112, first paragraph, an applicants' disclosure is not required to present specific test results such as *in vivo* or *in vitro* test results. All that is required under the statute is objective enablement. See, e.g., *In re Marzocchi et al.*, at 369:

> The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

The MPEP is also in agreement with the holding in *Marzocchi.* The MPEP states

that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The test for enablement is not whether any experimentation is needed but whether or not that experimentation is undue. See, *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976) in which the art involved (catalysis) was acknowledged to be unpredictable. Even a considerable amount of experimentation, or complex experimentation, is permissible if it is routine. See, e.g., *Ex parte Jackson,* 217 USPQ 804, 807 (POBA 1982) and *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

Merely because it is alleged that a specific example of treating a disease is not presented in the specification, one of ordinary skill in the art would not doubt the truth of the statements concerning the treatment of inflammation. As noted above, MPEP § 2164.02 states that compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. The nature of the invention and the state of the prior art, as discussed above, further demonstrate that applicants' specification provides sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention.

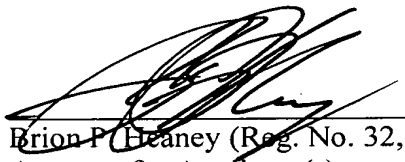
With respect to guidance, applicants' specification provides more than sufficient guidance with respect to dosages, formulations, modes of administration, and assays for determining the relative amount of PDE4 inhibitory activity. See, e.g., pages 53-59 and Examples 13-15.

Moreover, as the rejection focuses primarily on the scope of inflammatory diseases, applicants' disclosure provides more than sufficient guidance as to inflammatory disease that can be treated using PDE4 inhibitors. See, e.g., page 48, line 22-page 49, line 11. It is noted that these are the same inflammatory diseases that the art discloses can be treated using PDE4 inhibitors.

In view of the above remarks, it is respectfully submitted that applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with no more than routine experimentation. The rejection does not present sufficient reasons to doubt the veracity of the enabling statements set forth in the disclosure. Thus, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the above remarks, allowance of the instant application is respectfully requested. The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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